PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form (**http://bmjopen.bmj.com/site/about/resources/checklist.pdf**) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

ARTICLE DETAILS

TITLE (PROVISIONAL)	The effect of statins on average survival in randomised trials, an analysis of endpoint postponement
AUTHORS	Kristensen, Malene; Christensen, Palle; Hallas, Jesper

VERSION 1 - REVIEW

REVIEWER	Gabriel Chodick Tel Aviv University Israel
REVIEW RETURNED	21-Dec-2014

GENERAL COMMENTS	The authors used the endpoint postponement model to better demonstrate the average effect of therapy in RCTs compared to the popular NNT model. However, presenting the average effect of each treated patient using the endpoint postponement model in this case is conceptually and pragmatically problematic. a. Misleading presentation of the true effect: For the ordinary patient and many caregivers, postponement days may seem low, even in cases where the true effect is dramatic. For example, in the 4S study, statins extended life only in 32 days on the average. This result does not reflect the fact that statins reduced mortality rates by 30%, preventing approximately 70 deaths (among 2200 patients). In this aspect, a rare binary outcome such as death is lottery-like model where NNT fits well. b. Limited generalizability: Unlike relative risk estimates, postponement days (as well as attributable risk and NNT), depend heavily on follow-up duration and population absolute risk. Therefore, results from relatively short RCTs on low-risk populations, may yield seemingly low postponement days, even in cases where therapy was found very effective (e.g. a postponement of only 1.85 days in the JUPITER study). c. Underestimating therapy benefits in the post-intervention period: As the authors point out, the postponement-days model ignores benefits that may occur after trial's termination. . If my geometry is right, assuming a triangle shape survival curves, we should expect squared increase in the size of the effect for every doubling of follow-up duration. It would thus be interesting to calculate the expected extended life expectancy of a patient after 20 years of statins use. d. Complicated calculation: The methods described by the authors require the use of several graphical programs as well as rough assessment of figures. In addition, it is feasible only in articles where detailed survival curve are given. The quick method is applicable only where risk is constant over time, which is not always the case.

	e. Poor summary of therapy effect: As mentioned in Discussion, there are no good statistical analysis for pooling postponement days. It is clear that calculating median postponement days is insufficient and should be weighted for population size and study duration, as well as accompanied by 95% confidence intervals. Therefore, I think that the interesting postponement model might work better in models where disease-free time is important (e.g. time without gout attack, time without hypoglycemia, etc.) rather than the current one. Also, if the authors aimed at conducting a full meta-analysis, many parts are missing (including sub-population analysis, funnel plots, sensitivity analyses, etc. see PRISMA). Minor points 1. An example for calculating method might be helpful 2. Please add reference number in table 1 3. The study duration for CARDS 2004 was 4.75 years.

REVIEWER	Beatrice Alexandra Golomb, MD, PhD Professor of Medicine University of California, San Diego, USA
REVIEW RETURNED	09-Jan-2015

GENERAL COMMENTS	This manuscript examines expected average mortality benefit with statins in primary vs secondary prevention through the time of the study. The authors acceptably address the most relevant caveats: – the possibility that findings may differ in excluded trials (if anything, these appear likely a priori to be certainly no more favorable, given sources of presentation bias, and the authors affirm this likelihood based on mortality point estimates); – the possibility that findings may differ for other outcomes (these other outcomes are in any case less important, and do not objectively balance benefit and risk); – the possibility that benefits are not evenly distributed; – the possibility that findings might differ with longer term follow-up (however, any analysis considering this would necessitate major assumptions). These findings are critically important and merit publication. It will be helpful for both clinicians and patients to be more informed regarding what the expected survival benefit is in fact likely to be, in making deliberations regarding statin use, particularly in the face of adverse effect reports from patients.. A few minor comments are below: The authors mention possible limitations associated with confining analysis to the randomization period. It may bear mention that there are also important strengths associated with this: “Modeling” to estimate survival time beyond the treated time necessitates major assumptions. Studies like JUPITER (in which the trial was terminated early, without a clearly elaborated early stopping rule, “coincidentally” when the mortality curves appeared poised to cross) serve as a reminder that there is no guarantee that use beyond the time of the study will parallel effects of use for the time of

	the study. This remains true where there have been long term follow-up studies supporting benefit of the previously treated group. The interpretation of these is problematic for several reasons. (For one, since the use of statins in the follow-up period is not randomized, and the factors that lead people in the former statin-using to select to remain on, vs discontinue the drug are not known, and similar benefits might not have devolved to those who chose to discontinue the drug, had they remained on.) Analyses that compare survival benefit with long term follow-up from prior trial participants might be assessing the relative benefit of being a former statin user, as opposed to assessing benefit of length of treatment. (Those previously treated do not differ from those previously untreated, on current treatment). All-cause mortality rather than cardiovascular endpoints is the correct outcome to use because cardiovascular endpoints consider the benefit side of the risk-benefit equation, while all-cause mortality considers an outcome that objectively and equitably balances (fatal) risk and benefit1. Present trials do not have a useful proxy for all-cause serious morbidity (though, the former definition of serious adverse events served in that capacity)1, 2. In the concluding sentence it is stated that “statins are inexpensive and safe”. Both statements might benefit from some qualifier or caveat, though I do not insist on this. (On a population basis their recommended use is far from inexpensive. A more accurate statement is that their use may be usually safe, at least in clinical trial samples, and for the outcomes that the investigators chose to evaluate2, 3. Statins are commonly given, in the real world, to people with older age, comorbidities and polypharmacy, groups in whom they are substantially less safe4. The innumerable reported cases of statin-associated rhabdomyolysis, myositis, pancreatitis, autoimmune conditions, etc4, 5 are reminders that some risk is present, attending the modest gains. References 1. Statins and mortality. On the Risk. 2009;25(2):66-71. 2. The importance of monitoring statin adverse effects in statin, and other, clinical trials. Clin Invest. 2013;3(10):913-916. 3. Misinterpretation of trial evidence on statin adverse effects may harm patients. Eur J Prev Cardiol. 2014;published online 25 April 2014. 4. Statin adverse effects: a review of the literature and evidence for a mitochondrial mechanism. Am J Cardiovasc Drugs. 2008;8(6):373-418. 5. A Survey of the FDA's AERS Database Regarding Muscle and Tendon Adverse Events Linked to the Statin Drug Class. PLoS One. 2012;7(8):e42866.

REVIEWER	Huseyin Naci LSE Health, London School of Economics and Political Science, UK
REVIEW RETURNED	27-Feb-2015

GENERAL COMMENTS	In their submission Kristensen and colleagues estimated the average postponement of death in large statin trials that report Kaplan-Meier curves for all-cause mortality.

	The authors cite previous research that shows that patients and clinicians do not respond well to the “number needed to treat” measure. This difficulty in interpreting and communicating the NNT measure forms the primary motivation of the authors’ analysis. I agree with this premise, and applaud the authors for presenting the mortality benefits of statins in terms of endpoint postponement. However, I have a number of important questions and suggestions for the authors to consider. 1. The authors’ analysis is limited to mortality outcomes, which are clearly the most important endpoints for pharmacotherapy. However, as the authors acknowledge, the average postponement of death in the large trials of statins is very modest (which I agree is surprising). According to Halvorsen et al. Annals of Internal Medicine, 2007, in the 4S trial, simvastatin achieved an average 2-month postponement of heart attacks for all patients. It would be important to expand the primary analysis presented in this paper to include other key outcomes such as major coronary and cerebrovascular events. 2. Can the authors present their findings in an additional way to communicate the average length of event postponement for one individual among those who incurs benefits (similar to the NNT measure)? For example, in the 4S trial (Annals of Internal Medicine, 2007), simvastatin resulted in an average 8-month postponement of heart attacks for one of four patients. 3. The key limitation of the authors’ submission is that their analysis relied solely on the survival curves presented in the primary publications of the large statin trials. Accordingly, their analysis likely greatly underestimated the mortality benefits accrued over longer time periods. Why didn’t the authors’ consider the Heart Protection Study’s 11-year follow-up data, which to my knowledge is the longest running time among the large statin trials? This is available in Heart Protection Study Group, Lancet, 2011. 4. An interesting secondary analysis would be to estimate the average outcome postponement by the end of year 1, year 2, year 3, etc. for the all the available trials. This may explain the heterogeneity observed in the average findings at the end of trial follow up. 5. The final paragraph on the clinical implications of their study is very brief and adds very little to the current debate on statin pharmacotherapy in high-risk individuals. The authors may wish to expand on the key implications of risk communication and what a more routine analysis of outcome postponement would reveal as compared to other, more conventional, measures of treatment benefit.

VERSION 1 – AUTHOR RESPONSE

Reviewer 1

a. Misleading presentation of the true effect: For the ordinary patient and many caregivers, postponement days may seem low, even in cases where the true effect is dramatic. For example, in the 4S study, statins extended life only in 32 days on the average. This result does not reflect the fact that statins reduced mortality rates by 30%, preventing approximately 70 deaths (among 2200

patients). In this aspect, a rare binary outcome such as death is lottery-like model where NNT fits well.

Response:
Our very main point is that all of these measures of effect are technically correct, our postponement, the NNT and the relative risk reduction of 30% as the reviewer refers to. However, this seemingly large treatment effect of 30% mortality reduction does translate into a fairly short average postponement. This is not a flaw of our approach, but a simple consequence of the underlying figures. As for the lottery-like aspect, this is also covered in the introduction. In our understanding, it seems very plausible that statins would have an antiatherosclerotic effect in all treated. The understanding underlying the NNT is that e.g. one in forty has all the effect and the drug is completely wasted on the other treated, which is indeed very implausible. This is what we refer to as the lottery-like understanding.
We have given these deliberations a lot of space in the introduction and discussion and taken all relevant caveats. We find it difficult to elaborate it further, but will do so if the editor insists.

Change to manuscript:
None

b. Limited generalizability: Unlike relative risk estimates, postponement days (as well as attributable risk and NNT), depend heavily on follow-up duration and population absolute risk. Therefore, results from relatively short RCTs on low-risk populations, may yield seemingly low postponement days, even in cases where therapy was found very effective (e.g. a postponement of only 1.85 days in the JUPITER study).

Response:
Our response is similar to point a. The absolute net benefit of a short-running trial in a low-risk population is small, which is exactly what the postponement measure conveys.

Change to manuscript:
None

c. Underestimating therapy benefits in the post-intervention period: As the authors point out, the postponement-days model ignores benefits that may occur after trial's termination. . If my geometry is right, assuming a triangle shape survival curves, we should expect squared increase in the size of the effect for every doubling of follow-up duration. It would thus be interesting to calculate the expected extended life expectancy of a patient after 20 years of statins use.

Response
We fully agree with the reviewer that a considerable amount of postponement might be accrued after the trials' running time, at least if the survival curves are widely separated at the trials' termination. We have already elaborated that as a caveat. Estimating the benefit accrued after termination requires a lot of major assumptions, and simply assuming that the curves will continue to separate at the same rate, as the reviewer suggests, seems to be a particularly strong one, which is also contradicted by trial data (ref 26). It will fall outside the scope of our paper to develop and apply models for post-trial postponement. We have already referenced other authors in this respect.
See also comments from reviewer 2 and 3 below.

Change to manuscript
See response to reviewer 3

d. Complicated calculation: The methods described by the authors require the use of several graphical programs as well as rough assessment of figures. In addition, it is feasible only in articles

where detailed survival curve are given. The quick method is applicable only where risk is constant over time, which is not always the case.
Response:
We have already mentioned the “technical” caveat. As for the method using triangles, it does not require that the risk is constant over time. It is possible to graphically fit more than one triangle into a given area, which is obviously necessary if the survival curves cross each other.

Change to manuscript:
We have now explicitly stated that one or more triangles were fit into the area(s) between the curves in each study.

e. Poor summary of therapy effect: As mentioned in Discussion, there are no good statistical analysis for pooling postponement days. It is clear that calculating median postponement days is insufficient and should be weighted for population size and study duration, as well as accompanied by 95% confidence intervals.

Response
We fully agree, but as we already pointed out, no method has been developed to pool postponement estimates, primarily because there is no model for calculating the confidence intervals of postponement in the single study. The reviewer does not offer a solution.

Change to manuscript
It is now better explained why we cannot perform meta-analyses.

Therefore, I think that the interesting postponement model might work better in models where disease-free time is important (e.g. time without gout attack, time without hypoglycemia, etc.) rather than the current one. Also, if the authors aimed at conducting a full meta-analysis, many parts are missing (including sub-population analysis, funnel plots, sensitivity analyses, etc. see PRISMA).
Response:
Please see response above. We did not aim at a meta-analysis and had explicitly stated that this was not the case.

Change to manuscript.
None

Minor points
An example for calculating method might be helpful
Response:
A full, detailed example was already given in appendix B and duly referenced in the main text.

Change to manuscript:
None

Please add reference number in table 1
Change to manuscript:
Done

The study duration for CARDS 2004 was 4.75 years.
Change to manuscript:
Corrected in table 1. We use rounded figures, so the table reads “4.8”.

Reviewer 2
The authors acceptably address the most relevant caveats:
– the possibility that findings may differ in excluded trials (if anything, these appear likely a priori to be certainly no more favorable, given sources of presentation bias, and the authors affirm this likelihood based on mortality point estimates);
– the possibility that findings may differ for other outcomes (these other outcomes are in any case less important, and do not objectively balance benefit and risk);
– the possibility that benefits are not evenly distributed;
– the possibility that findings might differ with longer term follow-up (however, any analysis considering this would necessitate major assumptions).

These findings are critically important and merit publication. It will be helpful for both clinicians and patients to be more informed regarding what the expected survival benefit is in fact likely to be, in making deliberations regarding statin use, particularly in the face of adverse effect reports from patients..

A few minor comments are below:

The authors mention possible limitations associated with confining analysis to the randomization period. It may bear mention that there are also important strengths associated with this: "Modelling" to estimate survival time beyond the treated time necessitates major assumptions. Studies like JUPITER (in which the trial was terminated early, without a clearly elaborated early stopping rule, "coincidentally" when the mortality curves appeared poised to cross) serve as a reminder that there is no guarantee that use beyond the time of the study will parallel effects of use for the time of the study. This remains true where there have been long term follow-up studies supporting benefit of the previously treated group. The interpretation of these is problematic for several reasons. (For one, since the use of statins in the follow-up period is not randomized, and the factors that lead people in the former statin-using to select to remain on, vs discontinue the drug are not known, and similar benefits might not have devolved to those who chose to discontinue the drug, had they remained on.)

Analyses that compare survival benefit with long term follow-up from prior trial participants might be assessing the relative benefit of being a former statin user, as opposed to assessing benefit of length of treatment. (Those previously treated do not differ from those previously untreated, on current treatment).

Response
We fully agree with the reviewer on the above mentioned issues, but have chosen to not to elaborate further on these issues in order to keep focus on the main purpose of the paper.

Change to manuscript:
None

All-cause mortality rather than cardiovascular endpoints is the correct outcome to use because cardiovascular endpoints consider the benefit side of the risk-benefit equation, while all-cause mortality considers an outcome that objectively and equitably balances (fatal) risk and benefit1. Present trials do not have a useful proxy for all-cause serious morbidity (though, the former definition of serious adverse events served in that capacity)1, 2.

In the concluding sentence it is stated that "statins are inexpensive and safe". Both statements might benefit from some qualifier or caveat, though I do not insist on this. (On a population basis their

recommended use is far from inexpensive. A more accurate statement is that their use may be usually safe, at least in clinical trial samples, and for the outcomes that the investigators chose to evaluate2, 3. Statins are commonly given, in the real world, to people with older age, comorbidities and polypharmacy, groups in whom they are substantially less safe4. The innumerable reported cases of statin-associated rhabdomyolysis, myositis, pancreatitis, autoimmune conditions, etc4, 5 are reminders that some risk is present, attending the modest gains.

Response
We fully agree with the reviewer that the preferred outcome should be all-cause mortality. There are lots of reasons; if a cardiovascular benefit is offset – entirely or in part - by something else, it should be part of the picture. We also believe that all-cause mortality is much less prone to subjective classification than cardiovascular mortality.
Regarding the expense and safety of statins, we alluded to the expense for the individual patient. As the reviewer pointed out, expenses for statins are not exactly negligible from a society's perspective, but then again, neither are the benefits. We have used a single patient/clinician perspective in our discussion and would prefer to keep it this way, in order not to complicate the discussion unduly.

Change to manuscript:
We have modified the statements regarding expense and safety according to the reviewer's suggestion.

Reviewer 3

In their submission Kristensen and colleagues estimated the average postponement of death in large statin trials that report Kaplan-Meier curves for all-cause mortality.

The authors cite previous research that shows that patients and clinicians do not respond well to the "number needed to treat" measure. This difficulty in interpreting and communicating the NNT measure forms the primary motivation of the authors' analysis. I agree with this premise, and applaud the authors for presenting the mortality benefits of statins in terms of endpoint postponement. However, I have a number of important questions and suggestions for the authors to consider.

1. The authors' analysis is limited to mortality outcomes, which are clearly the most important endpoints for pharmacotherapy. However, as the authors acknowledge, the average postponement of death in the large trials of statins is very modest (which I agree is surprising). According to Halvorsen et al. Annals of Internal Medicine, 2007, in the 4S trial, simvastatin achieved an average 2-month postponement of heart attacks for all patients. It would be important to expand the primary analysis presented in this paper to include other key outcomes such as major coronary and cerebrovascular events.

Response
We have already acknowledged this as a limitation. However, we see the novelty of our paper as mainly a methodological one. To our knowledge, no one has performed a systematic review in this fashion. We believe the methodological case stands more clearly with just one defined outcome. An account of other outcomes than all-cause mortality would have greater interest if a method for meta-analysis of postponement is developed. Also, as pointed out by reviewer 2, all-cause mortality has a special interest in this case.
We will, however, comply if the editor insists. In that case, we would need to have our deadline extended.

Change to manuscript
None

2. Can the authors present their findings in an additional way to communicate the average length of event postponement for one individual among those who incurs benefits (similar to the NNT measure)? For example, in the 4S trial (Annals of Internal Medicine, 2007), simvastatin resulted in an average 8-month postponement of heart attacks for one of four patients.

Response
This possibility is mentioned in the discussion section as the hybrid model. Unfortunately, this model is highly if not purely speculative. There are no empirical clues to what proportion of the patients that has their endpoint postponed and what proportion that doesn't. In addition, there is only very limited experience in how a hybrid model is perceived by patients and how it affects their choices. There is good reason to suspect that few patients will grasp it intuitively.

Change to manuscript
We have extended the account of the hybrid model in the discussion section.

3. The key limitation of the authors' submission is that their analysis relied solely on the survival curves presented in the primary publications of the large statin trials. Accordingly, their analysis likely greatly underestimated the mortality benefits accrued over longer time periods. Why didn't the authors' consider the Heart Protection Study's 11-year follow-up data, which to my knowledge is the longest running time among the large statin trials? This is available in Heart Protection Study Group, Lancet, 2011.

Response
We cannot use this publication in our main analysis for two reasons; it does not provide a Kaplan-Meier curve of all-cause mortality, and the patients did not continue their randomized treatment after the trial's termination. In fact, there was an almost equal use of statins in the two groups after the end of the randomization period. However, the study does support the notion raised by reviewer 2 that the survival curves of the two groups tends to converge after the trial's termination.

Change to manuscript
The post-trial follow-up is now discussed using this paper as reference.

4. An interesting secondary analysis would be to estimate the average outcome postponement by the end of year 1, year 2, year 3, etc. for the all the available trials. This may explain the heterogeneity observed in the average findings at the end of trial follow up.

Response
Not a bad idea. However, there would be some technical problems in doing so. The graphs are typically dimensioned to show the entire course of the study, and focusing only on, say , the first year will result in a great deal of measurement error. Second, as we are not yet able to perform a meta-analysis on the postponement, the heterogeneity is less of a significant issue. Third, it is unlikely that much of the heterogeneity would be explained by different lengths of the trials. For example, it would not explain why some of the trials had negative postponements.
Although the idea is interesting, we believe that an analysis of postponement as a function of trial length would add a lot of text to the manuscript without adding much insight, but we will comply if the editor thinks otherwise.

Change to manuscript
None

5. The final paragraph on the clinical implications of their study is very brief and adds very little to the current debate on statin pharmacotherapy in high-risk individuals. The authors may wish to expand on the key implications of risk communication and what a more routine analysis of outcome postponement would reveal as compared to other, more conventional, measures of treatment benefit.

Response
We respectfully disagree with the reviewer regarding the clinical implications. Our advice may seem trivial at first glance, but from personal experience, we have seen many physicians tell their patients to continue their statin in spite of severe muscular complaints, essentially telling them that continuing statins is vital and that they had to live with their aching muscles. Our results support a more flexible attitude towards statin persistence, which needs to be spoken clearly.

Change to manuscript
The possibility of using postponement in communicating drug benefit to the patient is added.

VERSION 2 – REVIEW

REVIEWER	Gabriel Chodick Faculty of Medicine, Tel-aviv Universtiy, Israel
REVIEW RETURNED	19-Apr-2015

GENERAL COMMENTS	The autthors answered to all points raised.

REVIEWER	Beatrice A. Golomb, MD, PhD Professor of Medicine UC San Diego School of Medicine California, USA
REVIEW RETURNED	27-Apr-2015

GENERAL COMMENTS	This paper analyses the average expected survival gain with statins vs placebo in primary and secondary prevention by assessing the area between survival curves over the duration of the trial. The authors find that on average (and considering the median), survival gains are extremely small. They show that trials that did not include such curves were closely similar and if anything slightly less favorable in mortality odds ratios, so included trials are unlikely to materially misrepresent, particularly in an unflattering direction, the larger body of evidence. The study addresses an extremely important point. The methods are overall sound. The paper is written with great clarity. The finding is of high importance to patients and clinicians. Limitations are well reviewed. I have three points, all of which are clearly minor. 1. The statement “The median postponement of death for primary and secondary prevention trials were 3.2 and 4.1 days, respectively. “ belongs in What this study adds” together with the average findings in weeks, more than (or in addition to) in the Strengths and Limitations section. If only one value is given in the “what this study adds” it is more appropriate to provide the median than the “less than” with the most favorable figures provided. 2. In the discussion, it is stated that other outcomes like cardiovascular events could bear separate consideration with a

	similar analysis. I suggest that since cardiovascular events considers only the benefit side of the serious morbidity equation, that all-cause morbidity might be a more suitable outcome to mention. 3. The statement that suggests that guidelines should be kept the same may ease acceptance of the article (and for this reason, I will understand if the authors elect to preserve it), but the small magnitude of typical benefit as shown here, the nontrivial risk of adverse effects in real world use, and modern practices in which guidelines are often functionally enforced through factors like performance pay (so that doctors are incentivized to follow guidelines at the expense of patients, even if patients develop significant adverse effects) in my view go against preserving the present guidelines. I would as a minimum remove the word “severe” from the statement “However, if there are reasons for a patient not to take statins, for example severe muscular complaints, physicians should not be too insistent.” Overall, very well done.

REVIEWER	Huseyin Naci London School of Economics, UK
REVIEW RETURNED	12-Apr-2015

GENERAL COMMENTS	The authors addressed some of my comments with extremely minor modifications to the paper, and left the decision to address the remaining comments to the editor. Most importantly, I would urge the authors to expand their discussion about the clinical implications of their study, per my last comment (which the authors addressed by adding a single sentence): "The final paragraph on the clinical implications of their study is very brief and adds very little to the current debate on statin pharmacotherapy in high-risk individuals. The authors may wish to expand on the key implications of risk communication and what a more routine analysis of outcome postponement would reveal as compared to other, more conventional, measures of treatment benefit."

VERSION 2 – AUTHOR RESPONSE

Reviewer 1

The authors addressed some of my comments with extremely minor modifications to the paper, and left the decision to address the remaining comments to the editor.

Most importantly, I would urge the authors to expand their discussion about the clinical implications of their study, per my last comment (which the authors addressed by adding a single sentence): "The final paragraph on the clinical implications of their study is very brief and adds very little to the current debate on statin pharmacotherapy in high-risk individuals. The authors may wish to expand on the key implications of risk communication and what a more routine analysis of outcome postponement would reveal as compared to other, more conventional, measures of treatment benefit."

-We wish the reviewer had been more explicit about what he thinks we should have added. Our response last time read:

“We respectfully disagree with the reviewer regarding the clinical implications. Our advice may seem trivial at first glance, but from personal experience, we have seen many physicians tell their patients to continue their statin in spite of severe muscular complaints, essentially telling them that continuing statins is vital and that they had to live with their aching muscles. Our results support a more flexible attitude towards statin persistence, which needs to be spoken clearly.”

We have our reasons to prefer a postponement model as a mean of communicating benefit, mainly that patients are more responsive to a postponement model, i.e. their preferences depend on the presented values. We think these deliberations are already clearly presented and referenced in the text. We have little to add to the clinical implications.

-Change to manuscript:
We have added something about the technical difficulty of estimating postponement and added that researchers and guideline authors might aide the readers by using this technique in their publications.

Reviewer 3
1. The statement “The median postponement of death for primary and secondary prevention trials were 3.2 and 4.1 days, respectively. “ belongs in What this study adds” together with the average findings in weeks, more than (or in addition to) in the Strengths and Limitations section. If only one value is given in the “what this study adds” it is more appropriate to provide the median than the “less than” with the most favorable figures provided.

-Agreed and changed accordingly

2. In the discussion, it is stated that other outcomes like cardiovascular events could bear separate consideration with a similar analysis.
I suggest that since cardiovascular events considers only the benefit side of the serious morbidity equation, that all-cause morbidity might be a more suitable outcome to mention.

-An interesting suggestion. However, in practice it would be impossible to conduct such an analysis. How should one define such an outcome? Anything adverse or beneficial that happens to a patient? How should these be weighted?
Since our primary analysis is already focused on the benefit side of the coin and the adverse effects are somewhat briefly discussed in relation to these findings, we believe keeping this approach in this context would be reasonable.

-Change to the manuscript: none

3. The statement that suggests that guidelines should be kept the same may ease acceptance of the article (and for this reason, I will understand if the authors elect to preserve it), but the small magnitude of typical benefit as shown here, the nontrivial risk of adverse effects in real world use, and modern practices in which guidelines are often functionally enforced through factors like performance pay (so that doctors are incentivized to follow guidelines at the expense of patients, even if patients develop significant adverse effects) in my view go against preserving the present guidelines. I would as a minimum remove the word “severe” from the statement “However, if there are reasons for a

patient not to take statins, for example severe muscular complaints, physicians should not be too insistent."

-We firmly believe that current guidelines should not be changed because of our findings. Most adverse reactions towards statins are reversible, and given that statins are inexpensive and have a proven benefit (albeit small) with respect to survival and cardiovascular outcomes, it would seem a reasonable strategy to start using them if there is a good indication. Our results support the notion of having a low threshold for discontinuing if there are signs of intolerance or unpleasant side effects.

-Change to the manuscript
We have rephrased the last paragraph accordingly and removed "severe", also from the abstract.